B96 A meta-analysis toolbox for analyzing regional cortical functional organization

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ABSTRACT. Meta-analytic studies of the localization of cortical functions are faced with two problems:
(a) Visualizing activations reported as 3D coordinates (e.g. Talairach) in relation to cortical surface anatomy;
(b) Evaluating the statistical significance of differences in cortical activation foci in different categories of experiments. We describe the ***VAMCA*** toolbox (Visualization And Meta-analysis on Cortical Anatomy) that permits 3D activation foci to be mapped to a standardized representation of the inflated cortical surface and that statistically analyzes differences in location both on the cortical surface and in MNI space. *Three steps are involved.*
(1) Each 3D coordinate in MNI or Talairach space is transformed into Freesurfer spherical coordinates by identifying the cortical surface voxel nearest to the 3D coordinate in each of 60 normal, right-handed brains. The median location of those 60 cortical surface points is computed on a standardized hemispheric atlas.
(2) Topographic maps showing cortical surface foci locations on labeled average gyral and sulcal anatomy are displayed on Mollweide whole hemisphere projections for one or two different groups of studies. 3D foci distributions and median locations for two groups can also be visualized in MNI space.
(3) Cortical surface and 3D locations from two different categories of experiments or from two different conditions in a single experiment are statistically analyzed for group location differences using non-parametric permutation testing. A MatLab toolbox that includes cortical display tools and statistical tools and the anatomical database is available at www.ebire.org/hcnlab.

Goals and Methods: VAMCA can help users visualize probable cortical locations associated with MNI/Talairach 3D coordinates by building on the technique of multi-fiducial mapping [1]. VAMCA also provides formal tests for identifying cortical location differences for activations generated under different experimental conditions.

Subject database: Brain anatomical data from 60 right-handed, (18-48 y.o.) healthy subjects (33 male). 12 healthy, left-handed subjects (6 male) are also included.

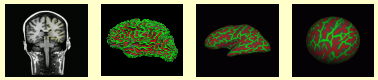
Processing: Freesurfer [2] generates cortical surfaces and registers them to a mean cortical surface. SPM5 segments and normalizes the T1 images to MNI-152 space using affine-only coregistration.

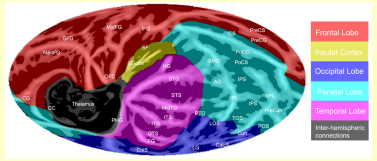
Multi-fiducial map database: 60 Normalized cortical surface space <-> 3D MNI space maps.

Cortical surface point averaging: An outlier-robust 2D median function averages the 60 cortical points corresponding to a single MNI coordinate to find a probable cortical surface location for each 3D coordinate. The 2D median function is also used to obtain a centroid for the surface points associated with a group of 3D foci.

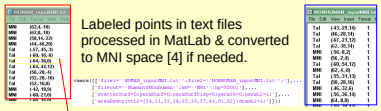
Group location difference tests: Two groups of surface-mapped 3D coordinates can be compared to test if they are in the same location. Permutation tests (inspired by [4]) are used to detect whether the surface distance between centroids (or point density in an ROI) of the two groups is unusually large compared to random group assignment (or random location assignment).

Example 1: Meta-analysis of Human vs. Non-human sounds in auditory cortex (See *Poster G86, Monday, for a full auditory meta-analysis*)

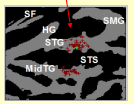




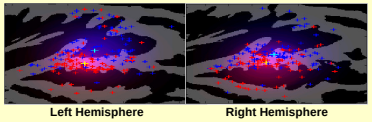
Hemisphere flat map centered on Auditory Cortex Showing gyral (light) and sulcal (dark) mean anatomy



Labeled points in text files processed in MatLab & converted to MNI space [4] if needed.

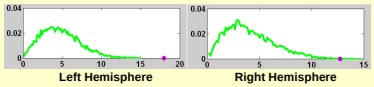


Multi-fiducial mapping of a point from 3D space to 60 individual cortical locations (red). Green cross is the 2D median location of the 60 points – the surface location used in subsequent processing.



Left Hemisphere **Right Hemisphere**

Red (Human sounds) and Blue (Non-human sounds) surface coordinate medians for *every* 3D point (foci) mapped on the cortical surface. The **group medians** are indicated in yellow (for red points) and cyan (for blue).



Left Hemisphere **Right Hemisphere**

The apparent mean separation of the two groups is tested using **a permutation test of the surface distance (mm) between the two group (Human vs. Non-human sounds) medians**. Actual group median distance (purple dot) & the probability distribution function (green) of group median distances when randomly assigning foci to groups. *The large distance suggests that human sounds are processed more laterally/inferiorly than are non-human sounds* (p<0.001 left hemisphere, and p=0.001 right hemi).

Anatomical Structure Abbreviations: **AG**, angular gyrus; **CC**, corpus callosum; **CG**, cingulate gyrus; **CalcS**, calcarine sulcus; **CoS**, collateral sulcus; **Cun**, cuneate; **CS**, central sulcus; **FG**, fusiform gyrus; **HG**, Heschl's gyrus; **IFG**, inferior frontal gyrus; **IPL**, inferior parietal lobule; **IPS**, intraparietal sulcus; **ITG**, inferior temporal gyrus; **ITS**, inferior temporal sulcus; **LG**, lingual gyrus; **LGofIn**, long gyrus of the insula; **LOS**, lateral occipital sulcus; **MedFG**, medial frontal gyrus; **MidFG**, mid-frontal gyrus; **MidTG**, middle temporal gyrus; **OFC**, orbitofrontal cortex; **OTS**, occipital temporal sulcus; **PCL**, paracentral lobule; **PHG**, parahippocampal gyrus; **POS**, parieto-occipital sulcus; **PoCG**, postcentral gyrus; **PoCS**, postcentral sulcus; **PreCG**, precentral gyrus; **PreCun**, precuneus; **PTO**, parietal/temporal/occipital point; **SF**, Sylvian fissure; **SFG**, superior frontal gyrus; **SMG**, supramarginal gyrus; **SPL**, superior parietal lobule; **STG**, superior temporal gyrus; **STS**, superior temporal sulcus; **TOS**, transverse occipital sulcus.

Validation of multi-fiducial averaging method.

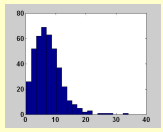
Q: Does VAMCA act as an inverse function to fMRI analysis output (cortical space --> MNI space)?
A: Yes, in fMRI a small number of subjects' activations are mapped from individual cortical anatomies to normalized 3D space and then averaged to produce MNI coordinates. VAMCA maps each MNI coordinate to 60 individual cortical anatomies and computes median locations on the cortical surface. *Monte Carlo analysis* verifies how well noisy, simulated cortical fMRI activations mapped to MNI space are reconstructed by VAMCA:

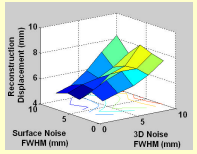
(a) **Simulated activations** are centered in various places across the normalized cortical hemisphere and mapped to the cortex for 10 randomly selected subjects in the database.

(b) **Location noise is added** to activation locations:
- *on the cortical surface* (to simulate activation/anatomical variability and surface registration errors);
- *also in 3D* after converting to the corresponding MNI coordinate (to simulate fMRI/anatomy coregistration error, MNI normalization error, and cluster location error).

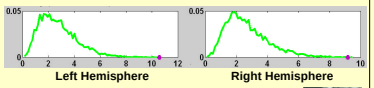
(c) Computed MNI coordinates are processed using VAMCA to **estimate cortical activation displacement**.

Results:

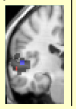




Left: Histogram of cortical displacements (mean 7.2 mm, median 5.9 mm) assuming 10mm FWHM of surface location noise and 6mm FWHM of 3D location noise.
Right: Median surface displacements (mm) for various 2D and 3D Gaussian location noise level combinations.

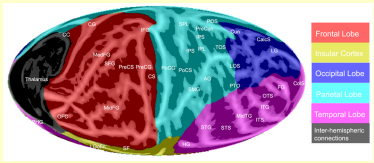


Left Hemisphere **Right Hemisphere**

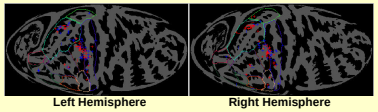


Above: A Permutation test in MNI space confirms the 3D separation (in mm) of the two sound groups' activation 3D medians. **Left:** Left hemisphere **3D median locations** in MNI space (Human sounds, Non-human sounds)

Example 2: Reanalysis of visually-triggered saccade activations vs. voluntarily-triggered saccade activations in the Frontal Lobe [5].



Hemisphere flat map for Association/Sensory/Motor Cortex centered on the central sulcus



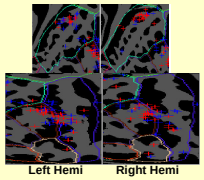
Left Hemisphere **Right Hemisphere**

Frontal lobe 3D foci from [5] obtained using Sleuth software [3] from *www.brainmap.org*. Visually-triggered saccades (red) and voluntarily-triggered saccades (blue) are shown.

Frontal lobe regions of interest (ROIs) defined by Freesurfer [2] on individuals, averaged on the mean flat map, and marked in different colors; include the ROIs:
Caudal Middle Frontal, **Lateral Orbital Frontal**, **Medial Orbital Frontal**, **Rostral Middle Frontal**, **Pars Operculus**, **Pars Triangularis**, **Paracentral**, **Precentral**, **Superior Frontal**

Testing the density (difference) of activations on surface regions of interest (ROIs) over a lobe.

A **permutation test on the location density of foci** over the frontal lobe ROIs shown above can be performed to test whether any **ROI contains an unusually large number of foci associated with at least one type of saccade**:



Left Hemi **Right Hemi**

Superior Frontal:
LH:p=0.009 (voluntary)
RH:p=0.006 (visual)
Precentral
LH:p=0.019 (voluntary)
RH:p=0.005 (voluntary)
Caudal Middle Frontal:
LH:p<0.001 (visual)
RH:p<0.001 (visual)

Another permutation test can be used to test if there is a **significant density difference between saccade types,** indicating more activation in the ROI for one condition.
ROIs of some significance:

Caudal Middle Frontal (Left): p=0.009	**Visual > Voluntary**
Caudal Middle Frontal (Right): p=0.058	**Visual > Voluntary**
Superior Frontal (Right): p=0.052	**Visual > Voluntary**
Precentral (Right): p=0.035	**Voluntary > Visual**

Use of coordinate weights to promote the robustness of the meta-analysis

Among the well-known problems with formal meta-analyses ([3],[5],[6]) are variations in statistical power between fMRI experiments. This can be tempered by varying the assumptions used in the preceding analyses via altering weights assigned to 3D coordinates used in computing both location medians and densities. E.g.:

- Assign the same total weight to every **experiment** and divide it evenly among all reported foci from the experiment (similar to an approach in [6]).
- Give greater weight to experiments with more **subjects**.
- Variations in post-processing affecting **cluster size and maximal z scores** can be countered by using 3D foci weights of cluster size or maximal z values, respectively.

Varying foci weights as suggested enhances robustness by allowing us to see if the varied weights do not substantially affect permutation test outcomes. E.g.:

Example 2: Robustness check for activation differences for two saccade conditions

p values for ROI foci density difference *Visual* > *Voluntary* saccades (ROIs with significant activations):

Weighting Type →	Foci (all weights=1)		Experiment (exp. sum=1)		Subjects (exp. sum=n)	
Hemisphere →	LH	RH	LH	RH	LH	RH
Caudal Middle Frontal	**0.009**	0.058	**0.003**	0.019	**0.013**	**0.008**
Precentral	-0.32	-0.035	-0.48	-0.093	-0.37	-0.085
Superior Frontal	-0.13	0.052	-0.10	0.059	-0.34	0.027

The **Caudal Middle Frontal** ROI in the **Left hemisphere** contains the only truly robust, significant density difference **Visual Saccade > Voluntary Saccade**.

Summary

- **Multi-fiducial mapping locates areas of possible cortical surface activation associated with published MNI or Talairach coordinates.**
- **Surface group medians locate likely centers of activation and can be used to locate groups of activations within ROIs.**
- **Permutation testing provides non-parametric tools for establishing group median location differences, activated ROIs, and activation differences in ROIs.**
- **Foci weightings can be used to provide a measure of robustness to the meta-analysis.**

References.

[1] van Essen, *Neuroimage*, **28**:635-662, 2005; Zacks, *J Cog Neuro*, **20**(1): 1-19, 2008.
[2] Dale, et al, *Neuroimage*, **9**:179-194, 1999; Fischl, et al, *Cereb. Cortex*, **14**, 2003.
[3] Laird, et al, *Hum. Brain Mapp.*, **25**:155-164, 2005; www.brainmap.org
[4] Lancaster, et al, *Hum. Brain Mapp.*, **28**:1194-1205, 2007; www.brainmap.org
[5] Grosbras, et al, *Hum. Brain Mapp.*, **25**: 140-154, 2005.
[6] Wager, et al, *Cog, Affect, Behav Neuro*, **3**(4): 255-274, 2003.